



Melbourne Office  
509 St Kilda Road Melbourne  
VIC 3004 Australia  
GPO Box 1285K Melbourne  
VIC 3001 Australia

Telephone +61 3 9243 8300  
Facsimile +61 3 9243 8333  
Facsimile +61 3 9243 8334  
ghmelb@griffithhack.com.au  
www.griffithhack.com.au

The Commissioner of Patents

13 September 2004

COPY

Madam

**IN THE MATTER OF International Patent Application No. PCT/AU2004/000253  
in the name of BIODIEM LTD  
Entitled GROWTH PROMOTION METHOD  
Our Ref: DAB:ST:FP19199**

We refer to the Written Opinion dated 6 April 2004. We enclose new pages 6, 7 and 27 to 29 to replace pages 6, 7 and 27 to 29 at present on file.

In response to Section V of the Opinion, it is submitted that present claims 1 to 25 possess inventive step in the light of references D1 to D8.

The Examining Authority has acknowledged that references D1 to D4 do not disclose the use of the compounds of the present invention as growth promoters. In this regard, we point out that D1 discloses the use of the present compounds in treating microbial infections. D3 discloses a single compound falling within the scope of present formula I, namely 4(e), as exhibiting broad spectrum antimicrobial activity against Gram Positive bacteria *Bacillus subtilis*, Gram Negative bacteria *Salmonella typhosa* and the yeasts *Saccharomyces cerevisiae* and *Candida albicans*.

Contrary to the Examining Authority's comments, it is submitted that D2 and D4 do not disclose use of the compounds of the present invention as antimicrobial agents. D2 describes compounds of the chemical class 1,3-benzodioxoles for use as agents for stabilising insecticidal phosphoric esters when present in an insecticide evaporator. D4 discloses some compounds falling within the scope of present formula I as having pesticidal and fungicidal activities and therefore being suitable for use as plant protecting agents. It will be appreciated by those skilled in the art that most plant protecting agents possessing pesticidal activities are highly toxic if applied either parenterally or topically to animals or humans. The toxicity of these pesticides is possibly due to the lipid content and the highly fluid nature of animal cell walls as distinct from the rigid and less permeable plant cell wall. Given this knowledge, it is submitted that a person skilled in the art would not expect that an effective plant pesticide would have potential as a growth promoting agent.

# GRIFFITH HACK

PATENT AND TRADE MARK ATTORNEYS

The Commissioner of Patents

13 September 2004

The Examining Authority then goes on to state that when references D1 to D4 which disclose the use of the present compounds of formula I as antimicrobial agents are combined with references D5 to D8 that claims 1 to 25 lack inventive step. For the reasons discussed above, we believe that only references D1 and D3 disclose the use of the present compounds as antimicrobial agents. We will now discuss references D5 to D8 in turn.

## D5

This reference discloses di-lower alkyl 1-(2-pyridinylthio)-1,2-hydrazine dicarboxylate N-oxides and their use as supplements to animal or poultry feeds for improving the growth of monogastric animals such as pigs, chickens, turkeys, pheasants, rabbits or horses. We note that the growth studies in the examples are limited to chickens and pigs.

Column 3, lines 13 to 18 states that these compounds have also been found to have "chemotherapeutic activity" against *C. albicans*, *S. aureus*, *S. faecalis* and *E. coli*. However, there is no evidence provided in this reference to support this chemotherapeutic activity.

It is submitted that the compounds disclosed in D5 are completely different in a structural sense from the present compounds. A person skilled in the art would therefore not expect the present compounds to be useful in promoting growth in the light of D5.

## D6

This reference discloses the use of antimicrobial enzymes such as oxidases and lysozymes as an alternative to antibiotics in feeds for animals. The background section of this reference at page 1, lines 15 to 21 states that other enzymes such as phytases, alpha-amylases, proteases,  $\beta$ -glycanases, endoxylanases and mannanases have been routinely used as food additives so as to improve growth and feed conversion ratio and to reduce environmental pollution caused by manure from pigs, poultry and fish. We also draw the Examining Authority's attention to page 1, line 22 to page 2, line 1 of the background which states that during the 1950s it was realised that the addition of small amounts of antibiotics to animal feed resulted in improved zootechnical results in monogastric animals. However, it also states that "the mode of action of these antibiotics on the improvement of growth and feed conversion ratio is still not fully understood". Accordingly, this reference does not teach that the promotion of growth is solely associated with antimicrobial action.

The animal feed composition described in this reference is completely different to that of the present invention. There are two enzymes required, one which breaks down the cell wall and the other which generates a compound that is toxic to bacteria such as hydrogen peroxide. The effect of the enzymes are preferably enhanced by the presence of one or more polyunsaturated fatty acids (PUFAs). Page 7, line 16 also states that "preferably the compositions of the invention do not contain any antibiotics". This reference does not disclose or suggest that a substituted nitrostyrene antimicrobial compound would be useful in

# GRIFFITH HACK

PATENT AND TRADE MARK ATTORNEYS

The Commissioner of Patents

13 September 2004

promoting growth. A person skilled in the art would therefore not consider this reference to be relevant to the present invention.

## D7

This reference discloses a feed composition for chickens, pigs and cattle containing an erythromycin derivative which promotes peristalsis but has decreased or absent antimicrobial activity (see column 1, lines 50 to 51; column 14, lines 24 to 25 and 64; and column 15, lines 8 to 9). On this basis, it is submitted that this reference clearly teaches away from the use of antimicrobial compounds in promoting growth.

## D8

This is a general review suggesting that antimicrobials can be given to animals in small amounts so as to increase growth promotion. Page 312 clearly indicates that the mechanisms for the effects on growth by antimicrobials is not known. It is concluded that the substantial economic benefit of growth promotants in animal feed is not outweighed by the risk to human health of development of a resistant strain. This reference is much more concerned about the use for therapeutic veterinary purposes of antibiotics which are also used in humans. This reference clearly teaches away from the present invention and we consider that there is no motivation to combine this reference with D1 and D3 to support a lack of inventive step objection.

In summary, we believe that references D5 to D8 teach away from the present invention for the following reasons:

- (i) It is usually antibiotics and not antimicrobials that have been indicated as being useful in promoting growth.
- (ii) Generally broad spectrum antibiotics have not been used for this purpose.
- (iii) The chemical classes of antibiotics/antimicrobials disclosed in these references are different from the present compounds and it would therefore not be obvious to a person skilled in the art to use the compounds of the present invention in promoting growth.

Amendments have been proposed in response to the objection raised under Section VIII.

# GRIFFITH HACK

PATENT AND TRADE MARK ATTORNEYS

The Commissioner of Patents

13 September 2004

---

It is requested that the objections raised in the Written Opinion be withdrawn.

Yours faithfully  
GRIFFITH HACK

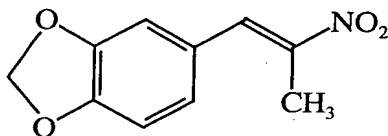
**Debbie Beadle**  
Principal  
[debbie.beadle@griffithhack.com.au](mailto:debbie.beadle@griffithhack.com.au)

alkyl.

Specific examples of the compounds of the present invention are as follows:

- 5 (1) X and Y are O, R<sub>1</sub> is methyl and R<sub>2</sub> to R<sub>7</sub> are hydrogen (3,4-methylenedioxy-β-methyl-β-nitrostyrene) (hereinafter referred to as "Iksin")

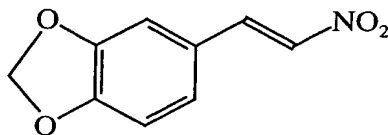
10



1

- 15 (2) X and Y are O and R<sub>1</sub> to R<sub>7</sub> are hydrogen (3,4-methylenedioxy-β-nitrostyrene)

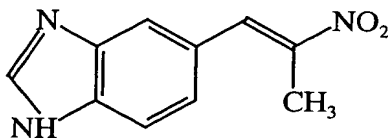
20



2

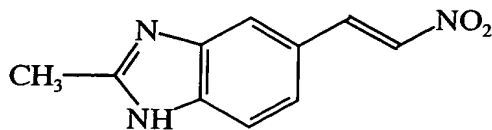
- 25 (3) X is N, Y is NH, R<sub>1</sub> is methyl, R<sub>2</sub> to R<sub>6</sub> are hydrogen and R<sub>7</sub> is absent (benzimidazole-5-β-nitropropylene)

30



3

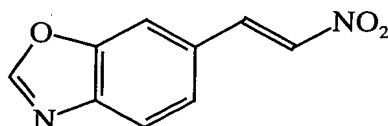
- (4) X is N, Y is NH, R<sub>1</sub> to R<sub>5</sub> are hydrogen, R<sub>6</sub> is methyl and R<sub>7</sub> is absent (2-methyl benzimidazole-5-β-nitroethylene)



5

4

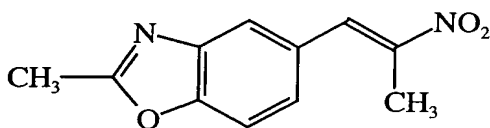
- (5) X is O, Y is N, R<sub>1</sub> to R<sub>6</sub> are hydrogen and R<sub>7</sub> is absent (benzoxazole-5-β-nitroethylene)



10

5

- (6) X is N, Y is O, R<sub>1</sub> is methyl, R<sub>2</sub> to R<sub>5</sub> are hydrogen, R<sub>6</sub> is methyl and R<sub>7</sub> is absent (2-methyl benzoxazole-5-β-nitropropylene)



20

6

By "pharmaceutically acceptable derivative" is meant any pharmaceutically acceptable salt, hydrate, ester, amide, active metabolite, analogue, residue or any other compound which is not biologically or otherwise undesirable and induces the desired pharmacological and/or physiological effect.

The salts of the compound of formula I are preferably pharmaceutically acceptable, but it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the present invention, since these are useful as intermediates in the preparation of pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts include salts of

mammal is a pig, cow or sheep and the bird is a chicken or turkey.

6. A method according to any one of claims 1 to 5,  
5 in which X and Y are either the same or different and selected from O and N.


7. A method according to claim 6, in which X and Y are both O.  
10

8. A method according to any one of claims 1 to 7,  
in which R<sub>1</sub> and R<sub>2</sub> are either the same or different and selected from hydrogen, hydroxy, halogen and optionally substituted C<sub>1-6</sub> alkyl.  
15

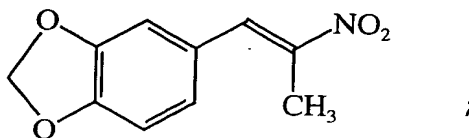
9. A method according to any one of claims 1 to 8, in which R<sub>3</sub> to R<sub>5</sub> are either the same or different and selected from hydrogen, hydroxy, halogen, nitro, C<sub>1-6</sub> alkoxy and optionally substituted C<sub>1-6</sub> alkyl.  
20

10. A method according to claim 8 or claim 9, in which the halogen is chlorine or bromine.

11. A method according to any one of claims 1 to 10,  
25 in which the compound of the formula I is in the form of an E isomer.

12. A method according to any one of claims 1 to 11,  
in which X, Y, , R<sub>6</sub> and R<sub>7</sub> are as defined in claim 1; R<sub>1</sub>  
30 and R<sub>2</sub> are either the same or different and selected from hydrogen, hydroxy, Cl, Br and C<sub>1-4</sub> alkyl; and R<sub>3</sub> to R<sub>5</sub> are either the same or different and selected from hydrogen, hydroxy, Cl, Br, nitro, C<sub>1-4</sub> alkoxy and C<sub>1-4</sub> alkyl.

13. A method according to any one of claims 1 to 12,  
35 in which X and Y are O, R<sub>1</sub> is methyl and R<sub>2</sub> to R<sub>7</sub> are hydrogen (3,4-methylenedioxy-β-methyl-β-nitrostyrene)

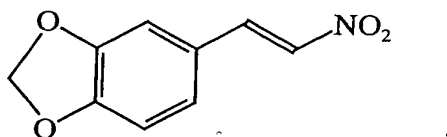


5

1

X and Y are O and  $\text{R}_1$  to  $\text{R}_7$  are hydrogen (3,4-methylenedioxy- $\beta$ -nitrostyrene)

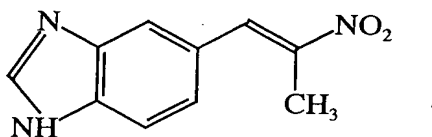
10



2

X is N, Y is NH,  $\text{R}_1$  is methyl,  $\text{R}_2$  to  $\text{R}_6$  are hydrogen and  $\text{R}_7$  is absent (benzimidazole-5- $\beta$ -nitropropylene)

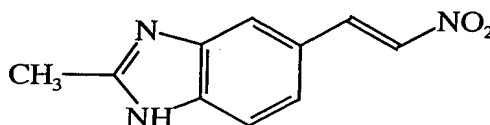
20



3

X is N, Y is NH,  $\text{R}_1$  is to  $\text{R}_5$  are hydrogen,  $\text{R}_6$  is methyl and  $\text{R}_7$  is absent (2-methyl benzimidazole-5- $\beta$ -nitroethylene)

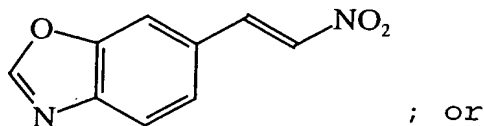
25



4

30 X is O, Y is N,  $\text{R}_1$  to  $\text{R}_6$  are hydrogen and  $\text{R}_7$  is absent (benzoxazole-5- $\beta$ -nitroethylene)

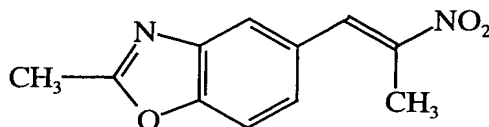
35



5



X is N, Y is O, R<sub>1</sub> is methyl, R<sub>2</sub> to R<sub>5</sub> are hydrogen, R<sub>6</sub> is methyl and R<sub>7</sub> is absent (2-methyl benzoxazole-5-β-nitropropylene)



6

14. Use of the compound of formula I as defined in  
10 any one of claims 1 to 13 in promoting growth of a  
subject.
15. Use of the compound of formula I as defined in  
15 any one of claims 1 to 13 in the manufacture of a  
medicament or feed for promoting growth of a subject.
16. A compound of formula I as defined in any one of  
claims 1 to 13 for use in promoting growth of a subject.
- 20 17. A composition for promoting growth in a subject,  
which comprises the compound of formula I as defined in  
any one of claims 1 to 13 and a carrier.
- 25 18. A pharmaceutical or veterinary composition  
comprising the compound of formula I as defined in any one  
of claims 1 to 13 and a pharmaceutically or veterinarily  
acceptable carrier.
- 30 19. A composition according to claim 18 which is a  
topical, oral or parenteral composition.
20. A composition according to claim 18 or claim 19  
in which the pharmaceutically or veterinarily acceptable  
carrier is an organic solvent.
- 35 21. A composition according to claim 20 in which the  
organic solvent is acetone, benzene, acetonitrile, DMSO or